Remarks

This Amendment is in response to the Office Action mailed October 11, 2006, in which the Patent Office rejected claims 1-13 of the application, all of the claims then pending. In this Office Action the Examiner also invited the applicants to amend the specification to reflect the status of the parent application, and interposed certain objections to the claims. Each of these matters are address below in the order presented in the Office Action.

I. Priority

As suggested by the Examiner, the specification has been amended to reflect that the parent of the present application, Ser. No. 10/048,872, is "abandoned."

II. Claim Objections

Claims 8-13 were objected to as improper, being multiple dependent claims depending from another multiple-dependent claim. Office Action, page 2. Claims 7, 8, 10 and 11 have been amended to remove multiple dependencies.

Claims 4-6 were objected to as failing to further limit the subject matter of the claim from which they depend, i.e., claim 3. Office Action, page 3. Claim 4 has been amended to delete the phrase "or the amino acid sequence of a derivative thereof with autoproteolytic activity," as suggested by the Examiner. Claims 5 and 6 have been amended to depend directly from claim 1. In depending from claim 1, claims 5 and 6 further limit the subject matter thereof by further specifying the structure of the "first polypeptide" recited in claim 1.

It is believed that these amendments address and obviate the objections to the claims, and withdrawal thereof is respectfully requested.

III. Double Patenting

Claim 13 was rejected on the ground of non-statutory obviousness-type double patenting, as being unpatentable over claims 1-9 of the commonly assigned U.S. Patent No. 6,936,455. Office Action, page 3-4. In the interest of advancing the prosecution of the present application, without conceding the correctness of the Patent Office's conclusion that obviousness-type double patenting exists between claim 13 of the present application and claims 1-9 of U.S. Patent No. 6,936,455, claim 13 is canceled without prejudice to pursuing the subject matter thereof in a continuing application. Cancellation of claim 13 renders with rejection moot.

IV. Rejections Under 35 U.S.C. § 112

A. Written description

Claims 1-13 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which is not described in the specification in such a way as to reasonably convey to one

skilled in the art that the inventors had possession of the claimed invention as of the time the application was filed. Office Action, pages 4-5. The Patent Office asserts that "the specification fails to exemplify or describe the preparation of the divergent pestivirus N^{pro} proteases commensurate in scope with the terms 'has the autoproteolytic function of' and 'derivative thereof with autoproteolytic activity.'" Office Action, page 4. According to the Patent Office,

> [t]hese terms recited in, e.g., claims 1 and 4-6, exceed deletions of the amino-proximal regions recited in claims 5 and 5 [sic, 6] and exceed the introduction of one or few amino acid substitutions because they reach derivatives that need have no particular, or limited, structural relationship to, e.g., the amino acid sequence set forth in SEQ ID NO: 1.

Id. The Patent Office asserts that "[w]here Wiskerchen et al. were able to identify an amino acid essential to the autoproteolytic activity of a pestivirus N^{pro} autoprotease, they were unable to identify a set of amino acids, and their relationship to the primary structure of a pestivirus N^{pro} autoprotease, that are sufficient to maintain autoproteolytic activity." Office Action, page 4. The Patent Office then asserts that "the specification provides no disclosure that supports the non-specific derivatization of pestivirus N^{pro} autoprotease amino acid sequences." Office Action, pages 4-5.

While the applicants agree that Wiskerchen teaches an amino acid that is essential for the activity of the BVDV autoprotease p20 (namely, Trp164), applicants note that there are substantial additional teachings in Wiskerchen regarding amino acids that are important for activity, but not absolutely critical (namely, His40 and His49), as well as at least one amino acid that is not important for activity (Ser124). Also, the applicants respectfully disagree with the Patent Office's position that there is no basis for the assertion that the present specification provides no support for derivatives of pestivirus N^{pro} autoprotease amino acid sequences. On the contrary, the present specification does identify regions within the peptide sequence that are key to the autoprotease activity of pestivirus N^{pro} autoproteases, namely the region Pro17 to Cys168, and especially Glu22 to Cys168. *See* Specification, paragraph bridging pages 6 and 7, and page 7, first paragraph. The specification identifies the C-terminal Cys as the cleavage site of the autoprotease. The specification also discloses that deletions and non-homologous substitutions of any, or all of the amino acids 2 to 21, and in particular 2-16, do not affect autoproteolytic activity. *See* Specification, page 6, second full paragraph; Example 2 (region 1-16 replaced by 10 amino acid poly-His sequence). The specification also discloses that the N-terminal amino acid, Met, is likely cleaved off by endogenous methionine aminopeptidase, and so is not critical to autoproteolytic activity of the peptide. *See, e.g.*, Specification, page 16.

Furthermore, the autoproteolytic activity of a pestivirus N^{pro} autoprotease is a well-defined functional characteristic. Pestivirus N^{pro} autoproteases are characterized by the ability to cleave a fused peptide between its own C-terminal cysteine residue and the N-terminus of the

fused peptide. Specification, page 3, fourth full paragraph. This distinquishes pestivirus N^{pro} autoproteases from, e.g., methionine autoproteases (MAP), which cleave N-terminal methionine (*c.f.*, Specification, pages 1-2), factor Xa protease, which cleaves at the tetrapeptide IleGluGlyArg (*c.f.*, Medabalimi, U.S. Patent No. 6,077,694, col. 2, ln 34-45), or non-specific peptidases such as trypsin. It known in the prior art (*e.g.*, from Wiskerchen) that there were specific amino acid substitutions and deletions that either abolish or retain the autoproteolytic activity of pestivirus autoprotease N^{pro} (as noted by the Patent Office at page 4 of the Office Action), and specifically that the His40 and His 49 residues were important (but not essential) for autoproteolytic activity, that the Trp164 was essential (Wiskerchen, page 4510, right column and page 4511, right column), and that replacement of Ser124 had no effect on activity (page 4510, right column). It also was well-known in the art as of the time the present application was filed that one can make homologous amino acid substitutions without substantially affecting protein function (*e.g.*, substitution of valine with leucine, which have aliphatic side chains that are adjacent homologs, or substitution of asparate with glutamate, which have acid side chains that are adjacent homologs, substitution of the adjacent amino side chain homologs asparagine and glutamine, etc.), as was the possibility of making "silent" substitutions in nucleic acid sequences that do not change the amino acid sequence of the encoded protein, and making such modifications to amino acid and nucleic acid sequences, as well as screening the results for a desired quality (such as the specific autoproteolytic activity of pestivirus N^{pro} autoproteases), were well within the ordinary skill in the art. Thus, a person having ordinary skill in the art would recognize from the specification that the applicants were in possession of the full scope of the claimed invention.

[redacted]

Id. The Patent Office contends that "[m]ere sequence perturbation cannot enable the design and preparation of polynucleotides encoding a myriad of divergent pestivirus N^{pro} autoprotease amino acid sequences that can provide the public with an auto protease retaining it native function as required by claim 1. *Id.*

Applicants respectfully disagree with the Patent Office's position. Patents are written to enable those skilled in the art to practice the invention. While § 112, first paragraph, requires that a patent must contain a description that enables one skilled in the art to make and use the claimed invention without undue experimentation, the fact that some experimentation is necessary does not preclude enablement, so long as the amount of experimentation is not unduly extensive for a person of ordinary skill in the art. *See, e.g.*, W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 U.S.P.Q. (BNA) 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851, 105 S. Ct. 172, 83 L. Ed. 2d 107, 53 U.S.L.W. 3239 (1984). The key is "undue," not "experimentation." *See*, In re Wands, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). The Court of Claims and Patent Appeals characterized "undue experimentation" as experimentation that would "require ingenuity beyond that to be expected of one of ordinary skill in the art." (In re Angstadt & Griffin, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976)), and the Board of Patent Appeals and Interferences has elaborated on this definition as follows:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.

Ex parte Jackson, 217 U.S.P.Q. 804, 807 (B.P.A.I. 1982).

In the present case, while some experimentation would be necessary to practice the claimed invention throughout its entire scope, perhaps even lengthy and tedious experimentation, the nature of the experimentation necessary does not "require ingenuity beyond that to be expected of one of ordinary skill in the art." The state of the art in the field of the present invention (as of the priority filing date of this application) was such that it was a matter of routine to sequence both nucleic acid molecules and polypeptides, and in the latter case to derive a nucleic acid sequence encoding that polypeptide. It was also a routine matter to identify within a nucleic acid sequence codons that could be replaced without altering the encoded amino acid sequence at all, as well as identifying amino acids within a polypeptide sequence (and consequently the corresponding codons) that could be substituted with amino acids having similar structural and physical properties (*e.g.*, substitution of valine with leucine, which have aliphatic side chains that are adjacent homologs, or substitution of asparate with glutamate, which have acid side chains that are adjacent homologs, substitution of the adjacent amino side chain homologs asparagine and glutamine, etc.), with the reasonable expectation

that the resulting polypeptide would substantially retain the properties (including activity) of the polypeptide from which it is derived.

The Patent Office suggests that it would require undue trial and error experimentation to practice the claimed invention. Office Action, page 6 ("Mere sequence perturbation canot enable the design and preparation of polynucleotides encoding a myriad of divergent pestivirus N^{pro} autoproteases ..."). However, the Federal Circuit has expressly rejected such a "trial and error" test for enablement:

> That was error. Assuming some experimentation were needed, a patent is not invalid because of the need for experimentation.

W.L. Gore v. Garlock, 220 U.S.P.Q. 303, 316 (Fed. Cir. 1983), cert. denied 469 U.S. 851 (1984).

Furthermore, with the advent of automatic synthesis and sequencing machines, it was a matter of routine experimentation to generate even enormous numbers of combinatorial nucleic acids based on defined parameters (*e.g.*, the nucleic acid sequence of a pestivirus N^{pro} autoprotease as a starting basis). Insertion and expression of such sequences in a host cell was likewise a matter of routine experimentation, as was the screening of the expressed proteins for a particular activity (*e.g.*, in a micro-array assay). The specification provides working examples of expression systems suitable for use in the present invention, and a detailed description to how to screen expressed peptides for the autoproteolytic activity of pestivirus N^{pro} autoprotease. *See*, generally, pages 5-9, and the Examples. The specification also provides direction as to which areas of the pestivirus N^{pro} autoprotease can be modified, or even entirely deleted, without significantly effecting the autoproteolytic activity thereof, including identification of the specific cleavage site after Cys168. *See, e.g.*, pages 4 and 6-7. The prior art (*e.g.*, Wiskerchen) provides additional teachings regarding which amino acids are, and are not, critical to the autoproteolytic activity of pestivirus N^{pro} autoproteases.

In view of the forgoing, the applicants submit that claims 2-4 and 7-12 are fully enabled by the specification, and respectfully request that this rejection be reconsidered and withdrawn.

C. Definiteness

Claims 1-13 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicants regard as their invention. Office Action, page 7.

The Patent Office asserts that the phrase in claim 1 "has the autoproteolytic function of" and the phrase in claims 4-6 "derivative thereof with autoproteolytic activity" render those claims indefinite because "the artisan and the public seeking to determine the metes and bounds of the intended subject matter cannot ascertain the structure of any derivatives from the specification's disclosure." The Examiner suggested deletion of the words "derivative thereof with autoproteolytic activity" from claims 4-6, and amendment of claim 1 to substitute "is a" for the

phrase "has the autoproteolytic function of." Claims 1-13 were rejected based on the Patent Office's conclusion that the phrase "polypeptide is connected to the ... polypeptide" did not clearly define the nature of the "connection;" the Examiner suggested amending the claims to recite "is covalently bound" to overcome this rejection. Claims 2, 3, 5 and 6 were further rejected because they recited acronyms; the Examiner suggested amending the claims to replace the acronym with the full name of the virus to overcome this rejection.

As suggested by the Examiner, claim 1 has been amended to recite "is a" instead of "has the autoproteolytic function of," claim 4 has been amended to delete the phrase "or the amino acid sequence ... autoproteolytic activity," and claims 2, 3, 5 and 6 have been amended to replace the acronyms with the full names of the viruses.

However, the applicants disagree that recitation of a functional limitation relating to the activity of the encoded peptide renders the claims indefinite in the present case. Claims 1 and 4-6 have been amended to recite "a derivative thereof having the autoproteolytic activity of a pestivirus N^{pro} autoprotease," which the applicants believe distinctly conveys to the artisan the metes and bounds of the claims. As discussed above with regard to the rejections of the claims under the first paragraph of § 112, claim 1 now specifically recites the structural nature of the autoproteolytic fusion partner. Further recitation of a derivative of a pestivirus N^{pro} autoprotease that retains the autoproteolytic activity thereof (*i.e.*, cleavage after a C-terminal Cys residue) distinctly defines the metes and bounds of the claim, in that the artisan would understand that the claim covers not only a pestivirus N^{pro} autoprotease, but also autoproteases that are derived therefrom by modifications such as deletion, insertion, substitution, N-terminal truncation, etc., that still retain that specific autoproteolytic activity.

The second paragraph of § 112 only that claims, when read in light of the specification, reasonably apprise those skilled in the art of the scope of the invention. *See, e.g.*, Miles Labs. v. Shandon, Inc., 997 F.2d 870, 27 USPQ2d 1123 (Fed. Cir. 1993), *cert. denied*, 510 U.S. 1100 (1994). Of course, an applicant is permitted to define an invention in functional terms, which in this case precisely define the metes and bounds of the term "derivative thereof" (*i.e.*, of a pestivirus N^{pro} autoprotease) by the readily understood and ascertainable criterion of possession of the "autoproteolytic activity of a pestivirus N^{pro} autoprotease."

In view of the forgoing, the applicants submit that the present claims fully meet the definiteness requirement of § 112, second paragraph, and respectfully request reconsideration and withdrawal of the rejections.

V. Rejection Under 35 U.S.C. § 102

Claim 1 has been rejected under 35 U.S.C. § 102(e) as being anticipated by Medabalimi, U.S. Patent No. 6,077,694. The Patent Office states that "[a]s noted above, claim 1 does not require that a protease having structure be encoded by a claimed nucleic acid molecule, thus

need not even be a pestivirus protease, an[d] need only have autoproteolytic activity." Office Action, page 9.

The applicants respectfully disagree with the Patent Office's position. "To anticipate, every element and limitation of the claimed invention must be found in a single prior art reference, arranged as in the claim." Brown v. 3M, 265 F.3d 1349, 60 USPG2d 1375 (Fed. Cir. 2001). Claim 1, as rejected, recited a nucleic acid molecule encoding a fusion protein comprising a first polypeptide *having the autoproteolytic function of an autoprotease N^{pro} of a pestivirus*, not merely "autoproteolytic activity." Thus, in order to anticipate, a prior art reference must, at a minimum, disclose a nucleic acid molecule encoding a fusion protein comprising a polypeptide having the autoproteolytic function of *an autoprotease N^{pro} of a pestivirus*.

Medabalimi does not disclose such a fusion protein. Medabalimi discloses a method for the efficient expression of fusion proteins having a retroviral autoprotease as a fusion partner. *See, e.g.*, col. 5, ln 16-20. This does not in and of itself suggest a nucleic acid molecule comprising any other specific autoprotease. While Medabalimi purports to teach expression of fusion proteins utilizing any autoproteolytic protease, it in fact discloses only the use in the invention of a specific retroviral "gag-pol" autoprotease that at cleaves at the sequence IleGluGlyArgPro. Col. 1, ln 46-58, Fig. 2, Example 1. This autoprotease has a very different activity (*i.e.*, specificity) than an autoprotease N^{pro} of a pestivirus, which cleaves at a Cys residue. Furthermore, Medabalimi specifically states that "the amino acids present in the cleavage site are specific to the protease being utilized for cleavage (col. 6, ln 26-28), making it clear that its general teaching of fusion proteins utilizing autoproteases does not, *per se*, literally or inherently teach the use of any and all autoproteases. *C.f.*, Corning Glass Works v. Sumitomo Elec., 868 F.2d 1251, 9 USPQ2d 1962 (Fed. Cir. 1989) (prior art genus does not inherently disclose all species falling within its scope).

In addition, claim 1 has now been amended to clarify that the first polypeptide is an autoprotease N^{pro} of a pestivirus, or a derivative thereof having the having the autoproteolytic activity of a pestivirus N^{pro} autoprotease. Thus, in addition to the functional limitations that are not disclosed in Medabalimi, claim 1 now contains structural limitations that clearly are not disclosed in Medabalimi. Reconsideration and withdrawal of this rejection is respectfully requested.

VI. Rejection Under 35 U.S.C. § 103

Claims 2-4 and 7-12 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Medabalimi as applied to claim 1, in further view of Wiskerchen et al. Medabalimi is acknowledged as not teaching the use of a pestivirus autoprotease, but is asserted to teach that "any autoprocessing protease will serve in the disclosed method." The deficiency in Medabalimi is asserted to be made up by Wiskerchen, which is said to teach that the pestivirus N^{pro}

autoprotease cleaves directly at its carboxy terminus. The Patent Office concludes that a person having ordinary skill in the art would have found it obvious to replace the HIV protease of Medabalimi with the pestivirus N^{pro} autoprotease of Wiskerchen to arrive at the invention of claims 2-4 and 7-12, which "require no particular structure." Office Action, page 10.

The applicants respectfully disagree with the Patent Office's position. Contrary to the Patent Office's assertion, claim 1, and by dependency claims 2-4 and 7-12, do in fact require a particular structure, *i.e.*, that of a pestivirus N^{pro} autoprotease, or a derivative thereof having the autoproteolytic activity of an N^{pro} autoprotease. Claims 2-3, even as originally filed, further specify that the pestivirus be CSFV, BDV or BVDV, and claim 4, even as originally filed, recites a specific amino acid sequence. Thus, claims 2-4 and 7-12 in fact do, and always have, contain specific structural limitations. In any even, claim 1, and by dependency claims 2-4 and 7-12, have been amended to expressly state this. As detailed above in response to the rejection under § 102(e) of claim 1, Medabalimi does not teach or suggest the use of any and all autoproteases in a fusion peptide, and in fact teaches that autoproteases recognize unique cleavage sites, and so are not freely interchangeable in a fusion protein. *C.f.*, In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992) (no rule "that regardless of how broad, a disclosure of a chemical genus renders obvious any species that happens to fall within it.").

Wiskerchen does not make up for this deficiency in Medabalimi. Contrary to the Patent Office's assertion, Wiskerchen does not teach the cleavage site of the BVDV N^{pro} autoprotease. *See*, page 4513, final paragraph ("Among the issues that require additional attention are ... determination of its cleavage site specificity ..."). Indeed, Wiskerchen does not even teach that the BVDV autoprotease is part of a defined class of autoproteases. *See*, page 4513, final paragraph ("Among the issues that require additional attention are establishment of the proteinase class to which p20 belongs ..."). Thus, Wiskerchen does not supply the necessary teachings that would suggest, or even permit, that a person of ordinary skill in the art as of the time of the application filing date could substitute the BVDV autoprotease for the retroviral autoprotease of Medabalimi, and there is neither a complete teaching or suggestion of the claimed invention, nor motivation for combining the Medabalimi and Wiskerchen references, nor a basis for a reasonable expectation of success in doing so.

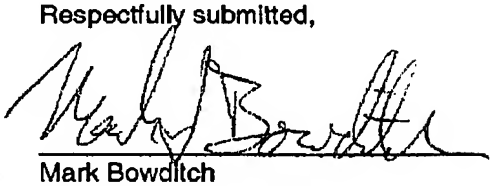
In view of the forgoing, the applicants submit that the invention of claims 2-4 and 7-12 is not obvious over the combination of Medabalimi and Wiskerchen, and respectfully request reconsideration and withdrawal of the rejection.

Conclusion

In view of the foregoing, the applicants respectfully submit that claims 1-12 of the present application are in condition for allowance. Reconsideration and withdrawal of the pending rejections, and favorable action on the claims, is earnestly solicited. Should any issues remain

that could be resolved via telephone conference and/or supplemental or examiner's amendment, the examiner is encouraged to contact the undersigned at (609) 627-8550.

Respectfully submitted,



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